DATA EVALUATION RECORD

TRIFLUMEZOPYRIM

STUDY TYPE: PRENATAL DEVELOPMENTAL TOXICITY STUDY – RABBIT
OCSPP 870.3700b [§83-3b]; OECD 414

MRID 49382177

Prepared for

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Task 6-169

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DATA EVALUATION RECORD[1]

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OCSPP 870.3700b [§83-3b]; OECD 414.

PC CODE: 129210 **DP BARCODE:** D432127

TEST MATERIAL (PURITY): Triflumezopyrim (99.4% a.i.)

SYNONYMS: DPX-RAB55 Technical; DPX-RAB55; 2,4-Dioxo-1-(5-pyrmidinylmethyl)-3-[3-(trifluoromethyl)phenyl-2*H*-pyrido[1,2-α]pyrimidium, inner salt.

CITATION: Charlap, J. (2013) An oral (gavage) prenatal developmental toxicity study of DPX-RAB55 technical in rabbits. WIL Research Laboratories, Inc. (Ashland, OH). Laboratory report number WIL-189256. June 20, 2013. MRID 49382177. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company (Wilmington, DE).

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 49382177), triflumezopyrim (99.4% a.i., lot no. SG0311647) was administered by oral gavage to 22 time-mated New Zealand White [Hra:(NZW)SPF] female rabbits/dose group on gestation days (GD) 7 to 28. Gavage doses in 0.5% methylcellulose (4000 cps) with 0.1% Tween® 80 were 0, 50, 100, 250, or 500 mg/kg/day. Maternal parameters included body weight, body weight gain (absolute and adjusted for the products of conception), food consumption, survival, clinical signs, hematology, reproductive outcomes, gravid uterine weights, organ weights, and gross pathology. Fetal parameters included the following: body weight, fetal sex ratios, number of live and dead fetuses, fetal resorptions, and incidences of external, visceral, head, and skeletal malformations and variations.

At 500 mg/kg/day, decreases in body weight gains and food consumption were observed in maternal animals; however, there was no effect on absolute body weight. One female in the 500 mg/kg/day group was euthanized *in extremis* on GD 26 due to body weight loss and markedly low food consumption; decreased defecation was also noted for this female. All other females survived to the scheduled necropsy.

[1] This DER was generated by modifying the study summary in a Tier II document (MRID 49382105).

The maternal NOAEL for triflumezopyrim in rabbits was 500 mg/kg/day, the highest dose tested. The maternal LOAEL was not established.

Intrauterine fetal growth and survival were unaffected by test substance administration at any dose level. There were no treatment-related fetal malformations or developmental variations observed.

The developmental NOAEL for triflumezopyrim in rabbits was 500 mg/kg/day, the highest dose tested. The developmental LOAEL was not identified.

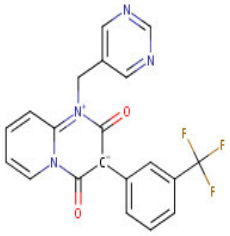
The developmental toxicity study in the rabbit is classified **Acceptable/Non-Guideline** because the study did not test up to the limit dose; however, it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Triflumezopyrim technical

Description:	Yellow powder
Lot #:	SG0311647
Purity:	99.4% a.i.
Compound stability:	Stable at room temperature. Expiry April 13, 2015.
CAS #:	1263133-33-0
Structure:	

2. Vehicle and/or positive control: 0.5 % Methylcellulose (4000 cps) with 0.1% Tween® 80 was used as the control and the vehicle for the preparation of the dosing formulations. No positive control was used.

3. Test animals:

Species:	Rabbits, time-mated females
Strain:	New Zealand White [Hra:(NZW)SPF]
Age/weight at study initiation:	Approximately 6 months old; 2.932–4.109 kg on GD 7
Source:	Covance Research Products, Denver, Pennsylvania, USA
Housing:	Animals were housed singly in stainless steel cages suspended above ground corn cob bedding (Pel O'Cobs®; the Andersons, Cob Products Division, Maumee, Ohio).
Diet:	PMI® Nutrition International, LLC Certified Rabbit LabDiet® (#5322), *ad libitum.* Kale (one leaf per occasion) was provided three times a week.
Water:	Filtered tap water, *ad libitum*
Environmental conditions:	**Temperature:** 19±3°C **Humidity:** 50±20% **Air changes:** 10/hr **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	2-6 days

B. PROCEDURES AND STUDY DESIGN

1. In-life dates: Start: October 19, 2012; End: November 16, 2012.

2. Mating: Mating was not required since time-mated female New Zealand White rabbits were obtained from the supplier on GDs 1, 2, 3, 4 or 5. The day on which mating was confirmed by the supplier was designated GD 0.

3. Animal assignment: Animals were assigned to control and experimental groups using a computerized randomization procedure designed to produce a homogeneous distribution of body weights across groups within each breeding lot, as indicated in Table 1.

TABLE 1. Animal assignment [a]					
Dose (mg/kg/day)	**0**	**50**	**100**	**250**	**500**
Number of females	**22**	**22**	**22**	**22**	**22**

[a] Data obtained from p. 22 of the study report (MRID 49382177).

4. **Dose selection rationale:** The dose levels were determined from results of a previous range-finding study in pregnant rabbits (WIL-189247; study report not provided) where doses of 0, 100, 250, and 500 mg/kg/day were used. Increased incidences of decreased defecation without corresponding effects on mean body weight parameters and food consumption were noted in the surviving females in the test substance-treated groups. At 250 mg/kg/day, 1 female was euthanized on GD 21, and 1 female each in the 100 and 500 mg/kg/day groups aborted on GDs 28 and 27, respectively. All 3 of the females experienced body weight losses, severely reduced food consumption, and decreased defecation prior to euthanasia/abortion. Based on these results, dose levels of 50, 100, 250, and 500 mg/kg/day were selected for this study.

5. **Dosage preparation:** Suspensions of test substance in 0.5% methylcellulose (4000 cps) with 0.1% Tween® 80 were prepared fresh on each day of dosing and stored at room temperature. The homogeneity and concentration of the dosing suspensions were checked by HPLC/UV analyses at the beginning and end of the study.

   Results:

   Homogeneity analysis: For all groups, the mean percent of target ranged from 95.8-103%, with RSD range of 3.3-6.6%.

   Concentration analysis: The mean concentrations of the formulations ranged from 89.2-101% of target. The test substance was not detected in the vehicle control.

   Stability analysis: Data were not presented in the current study. The study author stated that test formulations in the range of 1 to 150 mg/mL were shown to be stable for 1 day when stored at room temperature.

   Assuming that the results of the stability study were properly interpreted and reported, the analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by oral gavage on GDs 7-28, in a volume of 10 mL/kg of body weight/day. Dosing was based on the most recent body weight determination.

C. OBSERVATIONS:

1. **Maternal observations and evaluations:** All rabbits were observed twice daily for moribundity and mortality. Individual clinical signs were recorded once daily from the day of receipt through GD 29 (prior to dose administration during the treatment period). Animals were also observed for signs of toxicity approximately 1-hour post-dosing. All dams were weighed on GDs 0 and 5, and daily from 7-29. Food consumption was measured daily from GD 5-29. Blood was collected at necropsy from surviving non-fasted rabbits and evaluated for hematology parameters.

   All surviving rabbits were euthanized on GD 29 by an intravenous injection of sodium pentobarbital. The thoracic, abdominal, and pelvic cavities were opened by a ventral mid-line incision, and the contents were examined. The uterus and ovaries were exposed and excised; additionally, the uterus was weighed. The placentae were also examined. The following reproductive parameters were determined: pregnancy rate, early delivery rate, total resorption rate, mean number of implantations, live and dead fetuses, corpora lutea counts, and pup sex ratio. Uteri with no macroscopic evidence of implantation were opened and stained in 10% ammonium sulfide solution for detection of early implantation loss according to Salewski. The brain, kidneys, liver, ovaries, and spleen from each female were weighed and placed in 10% neutral-buffered formalin. Maternal tissues were collected and retained for possible future histopathologic evaluation. All animals that had an unscheduled death were necropsied and tissues were retained for possible future histopathologic evaluations.

2. **Fetal evaluations:** Each viable fetus was examined externally, individually weighed, euthanized by a subcutaneous injection of sodium pentobarbital, and subjected to a visceral examination. The detailed external examination of each fetus included, but was not limited to, an examination of the eyes, palate, and external orifices. The visceral examination used a modification of the Stuckhardt and Poppe fresh dissection technique to include the heart and major blood vessels. Each fetus was sexed by internal examination. Fetal kidneys were examined and graded for renal papillae development. Heads from all fetuses were examined by a mid-coronal slice. All carcasses were eviscerated and fixed in 100% ethyl alcohol, then macerated in potassium hydroxide and stained with Alizarin Red S and Alcian Blue for skeletal examination. Recognizable fetuses from animals that had an unscheduled death were examined externally, euthanized, and retained in 10% neutral-buffered formalin.

D. DATA ANALYSIS:

1. **Statistical analyses:** Parametric one-way ANOVA, followed by Dunnett's test, if significant, was used to analyze continuous data (e.g., maternal body weight, body weight change, food consumption, gravid uterine weights, hematology parameters, organ weights, numbers of corpora lutea, implantation sites and viable fetuses, and fetal body weights). Kruskal-Wallis nonparametric ANOVA test, followed by Dunn's test as appropriate, was used to analyze the following: mean litter proportions (% per litter) of prenatal data (viable and nonviable fetuses, early and late resorptions, total resorptions, pre- and post-implantation loss, and fetal sex distribution), total fetal malformations and variations, and each particular external, visceral, and skeletal malformation or variation. Where applicable, the litter was used as the statistical unit. Differences were considered significant at $p<0.05$ and $p<0.01$.

2. **Indices:** Intrauterine data were summarized on a group mean litter and proportional litter basis as exemplified below:

Group Mean Litter Basis:

$$\text{Post-implantation Loss/Litter} = \frac{\text{No. Dead Fetuses, Resorptions (early/late)/Group}}{\text{No. Gravid Females/Group}}$$

Proportional Litter Basis:

$$\text{Summation/Group (\%)} = \frac{\text{Sum of Post-implantation Loss/Litter (\%)}}{\text{No. Litters/Group}}$$

Where:

$$\text{Post-implantation Loss/Litter (\%)} = \frac{\text{No. Dead Fetuses, Resorptions (early/late)/Litter}}{\text{No. Implantation Sites/Litter}} \times 100$$

Fetal Morphological Examination

$$\text{Summation/Group (\%)} = \frac{\text{Sum of Viable Fetuses Affected/Litter (\%)}}{\text{No. Litters/Group}}$$

Where:

$$\text{Viable fetuses Affected/Litter (\%)} = \frac{\text{No. Viable Fetuses Affected/Litter}}{\text{No. Viable Fetuses/Litter}}$$

3. **Historical control data:** The historical control data contained in the report summarized data from 69 datasets with time-mated Kalamazoo New Zealand White rabbits collected from April 2006 through June 2009. Intrauterine parameter data from 1484 does examined at caesarean section were presented as overall means and ranges. The incidences of fetal external, visceral, and skeletal malformations and variations were collected from 12,222 fetuses and 1394 litters and presented as total number of fetuses (litters) affected and as percent per litter.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** One female in the 500-mg/kg/day group was euthanized *in extremis* on GD 26 due to body weight loss (402 g from GD 10-26) and markedly low food consumption (<10 g from GD 14-26); decreased defecation was also noted for this animal from GD 16 until euthanasia. All other animals survived to the scheduled necropsy. There was treatment-related decreased defecation at 500 mg/kg/day; the incidence (fetuses affected) were 0 (0), 2 (1), 7 (3), 3 (1), and 29 (5) at 0, 50, 100, 250, and 500 mg/kg/day, respectively. Other clinical findings not considered treatment-related included brown, red, and/or clear material and hair loss on various body surfaces, soft stool, and diarrhea; these were noted infrequently, similarly in the control group, and/or in a manner that was not dose-related. No treatment-related mortality or clinical signs were observed at 50, 100 or 250 mg/kg/day.

2. **Body weight:** Body weight and body weight gain data are summarized in Table 2. At 500 mg/kg/day, mean body weight gains tended to be lower than controls (not statistically significant at any interval), resulting in significantly reduced (26%) body weight gain for the

overall treatment period (GD 7-29). Mean absolute body weights and corrected mean body weights/gains were not affected.

TABLE 2. Representative mean (±SD) maternal body weight and body weight gain (g) [a]

Gestation Day or Interval	Dose (mg/kg/day)				
	0	50	100	250	500
# of Dams	22	20	22	21	20-21
Body weight					
GD 0	3176±223	3205±215	3174±211	3156±184	3178±231
GD 7	3321±245	3347±246	3302±225	3269±220	3366±277
GD 20	3595±217	3647±279	3561±279	3519±224	3548±279
GD 29	3743±208	3776±271	3704±235	3617±223	3681±310
Gravid uterine weight (g)	496±116	478±57	486±67	462±89	429±119
Corrected BW: GD 29 [b]	3247±222	3298±252	3218±206	3155±168	3251±258
Body weight gain					
GDs 7-10	53±62	87±97	70±96	42±88	20±102
GDs 10-13	51±53	78±49	76±47	66±39	35±61
GDs 13-20	171±60	135±73	113±92	143±70	128±113
GDs 20-29	149±89	129±64	143±99	98±114	111±136
GDs 7-29	422±79	428±136	402±150	348±98	311±187* (-26) [c]
Net BW change [d]	72.0±155	92.2±174	44.2±143	-0.9±110	76.0±225

[a] Data obtained from pp. 43-54 in the study report (MRID 49382177).
[b] Corrected BW = Body weight on GD 29- uterine weight.
[c] Numbers in parentheses are percent change from control, calculated by the Reviewer.
[d] Net BW change = (Body weight on GD 29- uterine weight) - BW on GD 0.
* Statistically different ($p < 0.05$) from the control.

3. **Food consumption:** Selected food consumption data are given in Table 3. At 500 mg/kg/day, food consumption was generally lower than the control group at intervals throughout the treatment period, with occasionally significant differences; overall, food consumption was significantly lower (-14%) during GDs 7-29. This difference generally corresponded to decreased defecation and lower mean body weight gains. There were no treatment-related differences in mean food consumption at 50, 100, or 250 mg/kg/day. Although occasional significant differences from the control group were noted at 100 and 250 mg/kg/day, the changes were generally transient and/or did not occur in a dose-related manner.

TABLE 3. Representative mean (±SD) food consumption (g/animal/day) [a]

Gestation Day or Interval	Dose in mg/kg/day (# of Does)				
	0 (22)	50 (20)	100 (22)	250 (21)	500 (20-21)
GDs 7-10	177±19	182±32	179±30	166±38	148±34* (-16) [b]
GDs 10-13	163±27	171±33	160±34	153±34	133±32* (-18)
GDs 13-20	168±26	165±33	150±43	150±35	142±43 (-15)
GDs 20-29	138±30	134±22	119±29	120±23	119±35 (-14)
Overall (GD 7-29)	157±18	157±26	143±29	140±17	135±24* (-14)

[a] Data obtained from pp. 59-60 in the study report (MRID 49382177).
[b] Numbers in parentheses are percent change from control, calculated by the Reviewer.
* Statistically different ($p < 0.05$) from the control.

4. **Postmortem results:**

a. Organ weights: Organ weight data are summarized in Table 4. At 500 mg/kg/day, treatment-related changes on organ weights consisted of significantly higher mean spleen weights (~30%, absolute and relative to brain weight); however, there was a lack of monotonic dose response and the change was within the variability of the measurement.

TABLE 4. Mean (±SD) organ weight data [a]

Organ	Dose in mg/kg/day (# of Does)				
	0 (22)	50 (20)	100 (22)	250 (21)	500 (20)
Brain weight (g)	9.44±0.52	9.58±0.66	9.49±0.38	9.52±0.59	9.73±0.54
Spleen: Absolute weight (g)	1.65±0.36	1.60±0.52	1.59±0.36	1.51±0.40	2.17±0.69** (32) [b]
Relative (g/100 g brain wt))	17.53±3.98	16.62±5.16	16.78±3.78	15.83±4.19	22.19±6.67* (27)

[a] Data obtained from pp. 76-78 in the study report (MRID 49382177).
[b] Numbers in parentheses are percent change from control, calculated by the Reviewer for relative spleen weight.
* Significantly different ($p<0.05$) from control.
** Significantly different ($p<0.01$) from control.

b. Hematology: Hematology data are summarized in Table 5. Changes observed at 500 mg/kg/day consisted of significantly lower mean red blood cell (7.4%) and eosinophil (36 to 43%) counts and higher MCV (3.4%), MCH (3.3%) levels, and reticulocyte (27 to 46%) counts, as well as a tendency to slightly lower hemoglobin (4.1%) and hematocrit (4.6%) levels. The magnitude of these changes were relatively small and within the variability of the measurements.

TABLE 5. Mean (±SD) hematology data [a]

Observation	Dose in mg/kg/day (# of Does)				
	0 (22)	50 (20)	100 (22)	250 (21)	500 (20)
Red blood cells (RBC, $10^6/\mu L$)	5.78±0.47	5.69±0.33	5.72±0.48	5.78±0.44	5.35±0.44** (-7.4) [b]
Hemoglobin (HGB, g/dL)	12.2±0.8	12.2±0.6	12.1±0.9	12.5±0.8	11.7±0.8
Hematocrit (HCT, %)	37.3±2.8	37.4±2.0	36.7±2.7	38.0±2.5	35.6±2.5
Mean corpuscular volume (MCV, fL)	64.5±2.1	65.7±2.4	64.2±2.8	65.9±2.3	66.7±2.4* (3.4)
Mean corpuscular hemoglobin (MCH, pg)	21.1±0.7	21.5±0.7	21.1±0.9	21.7±0.9	21.8±0.7* (3.3)
Reticulocytes (%)	1.1±0.5	1.3±0.4	1.2±0.3	1.1±0.3	1.6±0.6* (46)
Reticulocytes ($10^3/\mu L$)	66.6±34.3	71.1±22.6	66.2±20.6	64.4±20.0	84.3±34.1
Eosinophils (%)	1.4±0.4	1.3±0.4	1.1±0.5	1.1±0.5	0.9±0.3** (-36)
Eosinophils ($10^3/\mu L$)	0.07±0.02	0.06±0.02	0.06±0.02	0.05±0.02	0.04±0.02** (-43)

[a] Data obtained from pp. 67-73 in the study report (MRID 49382177).
[b] Numbers in parentheses are percent change from control.
* Significantly different ($p<0.05$) from control.
** Significantly different ($p<0.01$) from control.

c. Gross pathology: No treatment-related macroscopic findings were noted at necropsy.

5. Cesarean section data: Data collected at cesarean section are summarized in Table 6. There were no adverse treatment-related effects on reproductive parameters in this study.

TABLE 6. Cesarean section observations [a]					
Observation	**Dose (mg/kg/day)**				
	0	**50**	**100**	**250**	**500**
No. Animals assigned	22	22	22	22	22
No. Animals pregnant	22	20	22	21	21
Pregnancy rate (%)	100	91	100	95	95
No. Non-pregnant	0	2	0	1	1
Maternal wastage	0	0	0	0	1
Euthanized *in extremis*	0	0	0	0	1
No. aborted	0	0	0	0	0
No. Premature delivery	0	0	0	0	0
Total No. corpora lutea	204	192	207	189	180
(Corpora lutea/doe)	9.3±1.9	9.6±2.0	9.4±1.7	9.0±2.0	9.0±1.7
Total No. implantations	184	173	200	170	160
(Implantations/doe)	8.4±2.4	8.7±1.4	9.1±1.7	8.1±1.9	8.0±2.4
Total No. litters	22	20	22	21	20
Total No. live fetuses	181	164	188	166	151
(Live fetuses/doe)	8.2±2.3	8.2±1.4	8.5±1.7	7.9±1.8	7.6±2.5
Total No. dead fetuses **(Dead fetuses/doe)**	0	0	0	0	0
No. intrauterine deaths	3	9	12	4	9
Early	3	7	9	3	6
Late	0	2	3	1	3
Intrauterine deaths/doe	0.1±0.4	0.5±0.8	0.5±0.9	0.2±0.4	0.5±0.6
Early	0.1±0.4	0.4±0.7	0.4±0.7	0.1±0.4	0.3±0.5
Late	0±0	0.1±0.3	0.1±0.4	0.0±0.2	0.2±0.4
Litters with total resorptions	0	0	0	0	0
Mean fetal weight (g):	44.2±4.6	42.1±4.2	41.5±4.6	42.3±5.2	41.6±7.2
Males	45.3±4.9	43.1±4.9	42.1±5.0	43.2±5.7	40.8±5.2
Females	42.4±4.5	40.8±4.4	40.5±5.0	41.2±5.4	41.0±8.5
Sex ratio (% male)	54.4±16.1	51.8±14.8	52.6±18.3	48.4±14.5	50.0±23.6
Pre-implantation loss (%)	10.6±16.3	8.5±11.5	3.1±5.5	9.4±13.2	10.7±21.4
Post-implantation loss (%)	1.5±3.8	5.1±8.6	5.8±8.5	2.0±4.4	6.0±8.4

[a] Data obtained from pp. 79-82 in the study report (MRID 49382177).

B. DEVELOPMENTAL TOXICITY: The numbers of fetuses (litters) available for evaluation were 181 (22), 164 (20), 188 (22), 166 (21), and 151 (20) in the control, 50-, 100-, 250-, and 500-mg/kg/day groups, respectively. Malformations were observed in 3 (3), 4 (4), 5 (5), 2 (2), and 4 (4) fetuses (litters) in these same respective dose groups. The total percent per litter with variations was 61%, 62%, 73%, 72% and 61% in the same respective groups. There were no treatment-related malformations or development variations.

1. External examination: External abnormalities are summarized in Table 7a. There were no treatment-related fetal external abnormalities. External malformations were observed in 1 (1), 2 (2), 2 (2), 1 (1), and 0 (0) fetuses (litters) in the control, 50-, 100-, 250-, and 500-mg/kg/day groups, respectively; however, these malformations were not considered treatment-related due to the lack of a dose response, dissimilarity of the findings, and the limited number of fetuses affected by a given malformation. There were no external variations noted at any dose level.

TABLE 7a. External examinations [a]					
Observations	**Dose (mg/kg/day)**				
	0	**50**	**100**	**250**	**500**
No. Fetuses (litters) examined	181 (22)	164 (20)	188 (22)	166 (21)	151 (20)
Malformations					
No. Fetuses (litters) affected	1 (1) [b]	2 (2)	2 (2)	1 (1)	0 (0)
Exencephaly with open eyelids	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastroschisis	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Microphthalmia and/or anophthalmia	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Hemimelia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Ectrodactyly	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Syndactyly	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pinna malpositioned, small	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cleft palate	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Omphalocele	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Malrotated paw(s)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Hydrocelphly with dome head	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

[a] Data obtained from pp. 83-84 in the study report (MRID 49382177).

[b] Fetal (litter) incidence.

1. **Visceral examination:** Visceral abnormalities are summarized in Table 7b. No treatment-related effects on fetal visceral malformations or variations. Any findings were observed infrequently, similarly in the control group, in a manner that was not dose-related and/or were within the range of the WIL historical control data. A few non-treatment-related findings that were not classified as either a malformation or developmental variation were not included in the summary tables; these included renal papilla(e) that were not fully developed, dark red areas on the liver, and a cyst in the liver.

TABLE 7b. Visceral examinations [a]					
Observations	**Dose (mg/kg/day)**				
	0	**50**	**100**	**250**	**500**
No. Fetuses (litters) examined	181 (22)	164 (20)	188 (22)	166 (21)	151 (20)
Malformations					
No. Fetuses (litters) affected	3 (3) [b]	1 (1)	1 (1)	0 (0)	0 (0)
Diaphragmatic hernia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Lungs, lobular agenesis	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Malpositioned kidney	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Retroesophageal aortic arch	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Select Variations [c]					
Accessory spleen(s)	21 (11)	26 (14)	27 (13)	18 (1)	24 (10)
Major blood vessel variation	11 (6)	13 (9)	22 (9)	16 (8)	6 (6)
Heart, extra papillary muscle	7 (4)	6 (4)	11 (7)	5 (3)	7 (5)
Gallbladder absent or small	3 (3)	5 (4)	3 (3)	5 (3)	1 (1)
Retrocaval ureter	0 (0)	1 (1)	11 (6)	5 (1)	3 (1)
Liver, accessory lobule(s)	0 (0)	0 (0)	2 (1)	0 (0)	3 (1)

[a] Data obtained from pp. 83-84 and 90-91 in the study report (MRID 49382177).

[b] Fetal (litter) incidence.

[c] Variations that occurred as more than a single occurrence are included.

3. Skeletal examination: Skeletal malformations and select variations are summarized in Table 7c. There were no treatment-related fetal skeletal abnormalities. Findings were observed infrequently, similarly in the control group, in a manner that was not dose-related, at a low incidence, and/or were within the range of the WIL historical control data.

TABLE 7c. Skeletal examinations [a]

Observations	Dose (mg/kg/day)				
	0	50	100	250	500
No. Fetuses (litters) examined	181 (22)	164 (20)	188 (22)	166 (21)	151 (20)
Malformations					
No. Fetuses (litters) affected	0 (0)	2 (2) [b]	3 (3)	1 (1)	4 (4)
Skull anomaly	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Costal cartilage anomaly	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)
Sternebra malaligned, severe	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
Vertebral anomaly with or without rib anomaly	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Scapula, small	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Variations					
13th full rib(s)	56 (15)	53 (15)	65 (15)	50 (15)	33 (12)
13th rudimentary rib(s)	32 (17)	21 (13)	20 (12)	27 (17)	24 (12)
7th cervical rib(s)	0 (0)	1 (1)	6 (1)	1 (1)	7 (5)
27 presacral vertebrae	24 (8)	8 (5)	13 (8)	5 (4)	11 (4)
Sternebra(e) #5 and/or #6 unossified	11 (9)	17 (8)	22 (10)	24 (9)	24 (10)
Extra site ossification anterior to sternebra #1	1 (1)	1 (1)	7 (4)	7 (5)	3 (3)
Sternebra(e) malaligned, slight or moderate	0 (0)	0 (0)	2 (2)	0 (0)	1 (1)
Sternebra with thread-like attachment	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
Hyoid arch(es) bent	1 (1)	4 (2)	3 (3)	8 (6)	2 (2)
Accessory skull bone(s)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Spherical enlargement of the rib(s)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)

[a] Data obtained from pp. 83-84 and 90-91 in the study report (MRID 49382177).
[b] Fetal (litter) incidence.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: In the 500 mg/kg/day group, one female was euthanized *in extremis* on GD 26 due to test substance-related body weight loss and markedly low food consumption. Clinical findings (decreased defecation), lower mean body weight gains and food consumption, lower mean red blood cell and eosinophil counts, higher MCV and MCH levels, higher mean reticulocyte count and spleen weights were noted at 500 mg/kg/day. No test substance-related effects were noted at 250 mg/kg/day.

Therefore, a dosage level of 250 mg/kg/day was considered the no-observed-adverse- effect level (NOAEL) for maternal toxicity.

Based on the lack of effects on embryo-fetal development at any dosage level, the NOAEL for embryo-fetal toxicity was considered to be 500 mg/kg/day, the highest dosage level tested.

B. REVIEWER COMMENTS:

The reviewer agrees with the investigator's conclusion that no maternal toxicity was observed. Changes in hematological parameters at 500 mg/kg/day were observed; however, the magnitude of the effects were relatively small and within the variability of the measurements. Mean spleen weights were increased ~30% at this dose; however, there was a lack of a monotonic dose response and the change was within the variability observed for this measurement. Furthermore, there were no treatment-related macroscopic findings at any dose level. Therefore, these effects were not considered to be adverse.

The maternal NOAEL for triflumezopyrim in rabbits was 500 mg/kg/day, the highest dose tested. The maternal LOAEL was not established.

The reviewer agrees with the investigator's conclusion that no developmental toxicity was observed. Intrauterine fetal growth and survival were unaffected by test substance administration at any dose level. There were no treatment-related fetal malformations or developmental variations seen up to the highest dose tested (500 mg/kg/day).

The developmental NOAEL for triflumezopyrim in rabbits was 500 mg/kg/day, the highest dose tested. The developmental LOAEL was not established.

C. STUDY DEFICIENCIES: There were not effects seen up to the highest dose tested; however, the study did not test up to the limit dose (1000 mg/kg/day). As a result, the study was classified as non-guideline.